Tipranavir

Brand Name: Aptivus
Drug Class: Protease Inhibitors

Drug Description

Tipranavir is a nonpeptidic protease inhibitor (PI) belonging to the class of 4-hydroxy-5,6-dihydro-2-pyrone sulfonamides. [1]

HIV/AIDS-Related Uses

Tipranavir was approved by the FDA on June 22, 2005, for use in combination with other antiretroviral agents for the treatment of HIV infection in highly treatment-experienced adults.[2]

Tipranavir in combination with ritonavir is indicated for treatment of HIV-1 infected adults who have evidence of viral replication, are highly treatment experienced, or have HIV-1 strains resistant to multiple PIs. Use of other active agents in addition to the tipranavir and ritonavir combination is associated with a greater likelihood of treatment response. Genotypic and phenotypic testing or treatment history should be considered when prescribing tipranavir, as the number of baseline primary PI mutations affects the virologic response to tipranavir.[3]

Because of concerns regarding tipranavir's safety profile, physicians are cautioned to consider its use only in patients for whom other effective regimens are not available.[4]

The risk-benefit of tipranavir with ritonavir has not been established in treatment-naive adult or pediatric patients.[5] Pediatric formulations are currently being evaluated in HIV infected patients ages 2 to 18 years in Phase I, II, and III clinical trials. No pediatric results have been reported to date.[6] [7]

Pharmacology

Tipranavir is a nonpeptidic PI that inhibits processing of viral Gag and Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature virions. It demonstrates antiviral activity in vitro against a broad panel of HIV-1 group M, non-clade B isolates. Tipranavir antiviral activity decreases on average 3.75-fold in the presence of human serum. When used with other antiretrovirals in vitro, tipranavir was shown to be additive to antagonistic with other PIs, generally additive with non-nucleoside reverse transcriptase inhibitors and nucleoside reverse transcriptase inhibitors, and synergistic with the fusion inhibitor enfuvirtide.[8]

Absorption of tipranavir in humans is limited, although no absolute quantification of absorption is available.[9] To achieve effective plasma concentrations on a twice-daily dosing regimen, tipranavir must be coadministered with ritonavir. In a dose-ranging evaluation in 113 HIV uninfected male and female volunteers, there was a 29-fold increase in the geometric mean morning steady-state trough plasma concentrations of tipranavir following coadministration with ritonavir twice daily as compared with administration of twice-daily tipranavir alone.[10] Bioavailability of tipranavir is increased when taken with a high-fat meal. Tipranavir is more than 99.9% bound to plasma proteins. It is not known whether tipranavir is distributed into human cerebrospinal fluid or semen.[11]

Tipranavir is in FDA Pregnancy Category C. No adequate or well-controlled studies of tipranavir have been done in pregnant women. In laboratory animal studies, no teratogenicity was detected in pregnant rats and rabbits at exposure levels approximately 1.1-fold and 0.1-fold those of human exposure. Fetal toxicity was observed in rats at exposure levels approximately 0.8-fold those of normal human exposure. Tipranavir should be used during pregnancy only when the potential benefit justifies the potential risk to the fetus. An Antiretroviral Pregnancy Registry has been established to monitor the outcomes of pregnant women exposed to antiretroviral agents, including amprenavir. Physicians may register patients by calling 1-800-258-4263 or online at http://www.APRegistry.com.[12]

In vitro metabolism studies with human liver microsomes indicate that cytochrome P (CYP) 3A4 is the predominant CYP enzyme involved in tipranavir metabolism. The oral clearance of tipranavir decreased after the addition of ritonavir, which may represent diminished first-pass clearance of the drug at the gastrointestinal tract as

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Pharmacology (cont.)

well as the liver. Tipranavir metabolism in the presence of ritonavir is minimal. Administration of 14-C tipranavir to patients receiving tipranavir with ritonavir showed that unchanged tipranavir accounted to 98.4% or more of the total plasma radioactivity circulating at 3, 8, or 12 hours after dosing. Only a few metabolites were found in plasma, all at trace levels.[13] Administration of 14-C tipranavir to patients receiving tipranavir with ritonavir dosed to steady-state showed that 82.3% of radioactivity was excreted in feces, and 4.4% of the radioactive dose was recovered in urine.[14]

In two Phase III studies, multiple PI-resistant HIV-1 isolates from 59 highly treatment-experienced patients who received tipranavir and ritonavir and experienced virologic rebound developed amino acid substitutions associated with resistance to tipranavir. The most common amino acid substitutions that occurred in more than 20% of virologic failure isolates were L33/I/F, V82t, and I84V. Tipranavir resistance was detected at virologic rebound after an average of 38 weeks of tipranavir with ritonavir treatment with a median 14-fold decrease in tipranavir susceptibility. Cross resistance to PIs has been observed. Tipranavir-resistant viruses that emerged in vitro had decreased susceptibility to the PIs amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, and ritonavir but remained sensitive to saquinavir.[15]

Genotypic or phenotypic analysis of baseline virus may help determine tipranavir susceptibility before initiating treatment. Regression analyses of baseline or on-treatment HIV-1 genotypes from 860 highly treatment-experienced patients in Phase II and III studies demonstrated that mutations at the following 16 amino acid codons were associated with reduced virologic response at 24 weeks and/or reduced tipranavir susceptibility: L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D, or I84V. Analyses of virologic outcome by number of primary PI mutations present at baseline showed reduced response rates if five or more PI-associated mutations were present at baseline and participants did not receive enfuvirtide concomitantly with tipranavir with ritonavir.[16]

Adverse Events/Toxicity

Tipranavir coadministered with ritonavir has been associated with reports of both fatal and nonfatal intracranial hemorrhage. This combination has also been associated with clinical hepatitis and hepatic decompensation, including some fatalities. Extra vigilance is warranted in individuals with advanced HIV disease or those with chronic hepatitis B or hepatitis C virus coinfection, as these individuals have an increased risk of hepatotoxicity. Symptoms of hepatitis include fatigue, malaise, anorexia, nausea, jaundice, bilirubinemia, acholic stools, liver tenderness, or hepatomegaly.[17]

The most frequent adverse effects of tipranavir are diarrhea, nausea, fatigue, headache, and vomiting. (Because of the requirement for coadministration of ritonavir with tipranavir, see the individual drug record for ritonavir for that drug's potential adverse effects for more information.) Adverse effects leading to discontinuation of treatment were reported in 7.8% of individuals receiving tipranavir compared to 4.9% in the comparator arm.[18]

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during post-marketing surveillance in HIV infected patients receiving PI therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued PI therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made, and a causal relationship between PI therapy and these events has not been established.[19]

Mild to moderate rashes, including urticarial rash, maculopapular rash, and possible photosensitivity, have been reported in people receiving tipranavir with ritonavir. In Phase II and III trials, rash was observed in 14% of female participants and 8% to 10% of male participants receiving tipranavir with ritonavir. Additionally, in one drug interaction trial in healthy female volunteers administered a single dose of ethinyl estradiol followed by tipranavir with ritonavir, 33% of participants developed a rash. Rash accompanied by joint pain or stiffness,

Adverse Events/Toxicity (cont.)

throat tightness, or generalized pruritus has been reported in both men and women receiving tipranavir and ritonavir.[20]

Increased bleeding, including spontaneous skin hematomas and hemarthrosis, have been observed in patients with hemophilia type A and B treated with PIs. In some patients, additional factor VIII was required. In many of the reported cases, treatment with PIs was continued or reintroduced if treatment had been discontinued. A causal relationship between PI therapy and these episodes has not been established.[21]

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including tipranavir. During the initial phase of combination antiretroviral treatment, a patient whose immune system improves may develop an inflammatory response to indolent or residual opportunistic infections, such as Mycobacterium avium infection, cytomegalovirus infections, Pneumocystis jirovecii pneumonia, or tuberculosis. Symptoms of immune reconstitution syndrome necessitate further evaluation and treatment.[22]

Redistribution of body fat, peripheral wasting, facial wasting, breast enlargement, and cushingoid appearance have been observed in patients receiving antiretroviral therapy.[23]

Treatment with tipranavir and ritonavir has resulted in large increases in the concentration of total cholesterol and triglycerides. Cholesterol and triglyceride testing should be performed prior to initiation of tipranavir and ritonavir therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate.[24]

Drug and Food Interactions

Bioavailability of tipranavir increases when taken with a high-fat meal. Antacids reduce absorption of tipranavir, requiring timing adjustments of antacid use. When tipranavir coadministered with ritonavir was given with 20 ml of aluminum and magnesium-based liquid antacid, tipranavir concentration under the concentration-time curve (AUC), peak plasma concentrations (Cmax), and serum concentration at 12 hours after dosing were reduced by 25% to 29%. Consideration should be given to separating tipranavir with ritonavir dosing from antacid administration to prevent reduced absorption of tipranavir.[25]

Tipranavir coadministered with ritonavir at the recommended dosage is a net inhibitor of CYP3A and may increase plasma concentrations of agents that are primarily metabolized by this enzyme. Coadministration of tipranavir with ritonavir with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious or life-threatening events is contraindicated. These drugs include amiodarone, bepridil, flecainide, propafenone, quinidine, astemizole, terfenadine, rifampin, dihydroergotamine, ergonovine, ergotamine, methylergonamine, cisapride, St. John's wort, lovastatin, simvastatin, pimozide, midazolam, and triazolam.[26]

Dose adjustments for abacavir, enteric-coated didanosine, or zidovudine may be necessary if these antiretrovirals are administered with tipranavir and ritonavir. Concurrent use of abacavir and tipranavir with ritonavir causes abacavir's AUC to decrease by about 40%. Clinical relevance of this reduction in abacavir AUC is not established, and dose adjustment of abacavir cannot be recommended at this time. Concurrent use of didanosine and tipranavir with ritonavir causes serum concentrations of didanosine to decrease. Clinical relevance of this reduction in didanosine AUC is not established. For optimal absorption, didanosine should be separated from tipranavir and ritonavir dosing by at least 2 hours. Concurrent use of zidovudine and tipranavir with ritonavir causes zidovudine's AUC to decrease by about 35%. Clinical relevance of this reduction in AUC is not established, and dose adjustment of zidovudine cannot be recommended at this time.[27]

A decrease in serum concentrations of amprenavir, lopinavir, or saquinavir is observed when any of these drugs are administered with tipranavir and ritonavir; combining any of these other PIs with tipranavir and ritonavir is not recommended. No formal drug interaction data are currently available for the concomitant use of tipranavir and ritonavir

Drug and Food Interactions (cont.)

with PIs other than amprenavir, lopinavir, or saquinavir.[28]

Fluconazole increases tipranavir concentrations when fluconazole is administered concurrently with tipranavir and ritonavir, but dose adjustments are not needed. High doses of azoles (e.g., fluconazole, itraconazole, ketoconazole, voriconazole) above 200 mg/day are not recommended for patients taking tipranavir with ritonavir. Because of the multiple enzymes involved in voriconazole metabolism, it is difficult to predict the drug-drug interactions between voriconazole and tipranavir with ritonavir.[29]

No dose adjustment of clarithromycin is necessary when clarithromycin is administered concurrently with tipranavir and ritonavir in patients with normal renal function. However, with patients with renal impairment, dosage adjustments should be made. For patients with creatinine clearances (CLCR) of 30 to 60 ml/min, the dose of clarithromycin should be reduced by 50%; for patients with CLCR of less than 30 ml/min, the dose of clarithromycin should be reduced by 75%. In a single-dose study of rifabutin with tipranavir and ritonavir, rifabutin and desacetyl-rifabutin serum concentration levels increased. Dosage reductions of rifabutin by 75% are recommended (e.g., 150 mg every other day). Increased monitoring for adverse events in patients receiving these drugs concurrently is warranted; further dosage reduction may be necessary.[30]

Concomitant use of trazodone and tipranavir with ritonavir may increase plasma concentrations of trazodone, leading to nausea, dizziness, hypotension, and syncope. A lower dose of trazodone should be considered in patients who require this combination of drugs. Dosage reduction and concentration monitoring of desipramine is recommended.[31]

Tipranavir and ritonavir with selective serotonin reuptake inhibitors (SSRIs) sertraline, paroxetine, or sertraline should be taken concomitantly with caution. Antidepressants have a wide therapeutic index, but doses may need to be adjusted upon initiation of tipranavir with ritonavir therapy.[32]

Plasma concentrations of calcium channel blockers (e.g., felodipine, nifedipine, nicardipine, nisoldipine, verapamil) may increase when given concurrently with darunavir and ritonavir. Caution is warranted and clinical monitoring of patients is recommended.[33]

Tipranavir capsules contain alcohol that can produce disulfiram-like reactions when coadministered with disulfiram or other drugs which produce this reaction (e.g., metronidazole). This combination should be prescribed with caution.[34]

The HMG-CoA reductase inhibitor atorvastatin should be administered with careful monitoring if being given concurrently with tipranavir and ritonavir. Doctors should also consider other HMG-CoA reductase inhibitors. Concomitant use of either lovastatin or simvastatin with tipranavir and ritonavir is not recommended.[35]

Careful glucose monitoring is warranted when tipranavir and ritonavir is administered concurrently with hypoglycemics (e.g., glimepiride, glipizide, glyburide, pioglitazone, repaglinide, tolbutamide).[36] More frequent concentration monitoring of immunosuppressants (e.g., cyclosporine, sirolimus, tacrolimus) is warranted until blood levels of the immunosuppressant have been stablilized, if these drugs are given concurrently with tipranavir and ritonavir.[37]

Concomitant use of fluticasone propionate and tipranavir with ritonavir may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Coadminstration of these drugs is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.[38]

Dosage increase and long-term use of meperidine are not recommended due to increased concentrations of the metabolite normeperidine, which has both analgesic and CNS stimulant activity (e.g., seizures). Dosage of methadone may need to be increased when it is coadministered with tipranavir and ritonavir. Methadone serum concentrations have decreased by 50% in the presence of tipranavir and ritonavir.[39]

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Drug and Food Interactions (cont.)

Alternative methods of contraception should be considered for women taking estrogen-based oral contraceptives concurrently with tipranavir and ritonavir, as ethinyl estradiol concentrations decrease by 50% when these contraceptives are taken with tipranavir and ritonavir. Patients using estrogens as hormone replacement therapy should be clinically monitored for estrogen deficiency.[40]

Concomitant administration of tipranavir and ritonavir with PDE-5 inhibitors, including sildenafil, vardenafil, and tadalafil, should be done with caution. PDE-5 inhibitor dosing should not exceed the doses as indicated by the manufacturer.[41]

The drug-drug interactions between warfarin and tipranavir with ritonavir cannot be predicted because of the conflicting effect of tipranavir and ritonavir on CYP2C9. Frequent monitoring upon initiation of tipranavir and ritonavir therapy is recommended.[42]

Contraindications

Tipranavir is contraindicated in individuals with known hypersensitivity to any of the ingredients in this product. It is also contraindicated in individuals with moderate to severe (Child-Pugh Class B and C, respectively) hepatic insufficiency.[43]

Clinical Trials

For information on clinical trials that involve Tipranavir, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Tipranavir AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[44]

Dosage Form: Capsules containing tipranavir 250 mg.[45]

The recommended dose of tipranavir is 500 mg (two 250 mg capsules) taken with ritonavir 200 mg twice daily with food. Bioavailability is increased with a high fat meal.[46]

Storage: Store capsules at 2 C to 8 C (36 F to 46 F) prior to opening the bottle. After opening, store at 25 C (77 F); excursions permitted to 15 C to 30 C (59 F to 86 F). Use within 60 days of opening the bottle.[47]

Chemistry

CAS Name: 2-Pyridinesulfonamide, N-(3-((1R)-1-((6R)-, 6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl) propyl)phenyl)-5-(trifluoromethyl)-[48]

CAS Number: 174484-41-4[49]

Molecular formula: C31-H33-F3-N2-O5-S[50]

C 61.78%, H 5.52%, F 9.46%, N 4.65%, O 13.27%, S 5.32%[51]

Molecular weight: 602.7[52]

Physical Description: White to off-white to slightly yellow solid.[53]

Solubility: Freely soluble in dehydrated alcohol and propylene glycol; insoluble in aqueous buffer at pH 7.5.[54]

Other Names

PNU 140690E[55]

PNU 140690[56]

U 140690[57]

TPV[58]

Further Reading

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Manufacturer Information

Tipranavir
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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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